MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: July 18, 2001

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: Metabolic and Endocrine Advisory Committee for NDA 21-332, Symlin (pramlintide)

SUBJECT: Overview of issues to be discussed at July 26, 2001 Advisory Committee meeting

On July 26, 2001, the Metabolic and Endocrine Advisory Committee will convene to discuss the data addressing the safety and efficacy of Symlin (pramlintide) for use as an adjunct to insulin therapy in patients with Type 1 and Type 2 diabetes. This memorandum is intended to outline the major issues about which we will be asking for input and comment from the committee.

Symlin (pramlintide) is an analogue of an endogenous pancreatic peptide and is intended for use in conjunction with insulin as a pre-mealtime subcutaneous injection. The drug has been studied in placebo-controlled studies in both Type 1 and Type 2 diabetics. The effect of pramlintide vs. placebo used in conjunction with insulin on HbA1c has been examined in the pivotal trials of safety and effectiveness.

The package that you have received contains, in addition to the day's agenda and a list of the committee members and consultants, the following: the review of clinical efficacy, a separate review of clinical safety, the statistician's review, the clinical pharmacologist's review, and the preclinical pharmacology/toxicology review. We have also forwarded draft questions to you under separate cover.

In addition to whatever questions you may raise after reading the briefing documents and hearing the presentations, we would like you to address several issues in your discussion. You will be asked if the data presented establish the efficacy of pramlintide, i.e., that it is superior to placebo with regard to change from baseline in HbA1c, for the proposed indications. In addition, and very importantly, you will be asked whether the studies were adequate by their design to shed light on the efficacy of pramlintide as an adjunct to insulin under conditions of therapy (with insulin, specifically) to achieve optimal glycemic control. In other words, does the clinical data package permit us to extrapolate efficacy to use in patients striving for HbA1c levels according to clinical practice guidelines?

Next, you will be asked about the adequacy of the trials to define the safety profile of the product. And again, this question will be followed with a request for input on the adequacy of the trials, by their design, to guide the safe use of the product under conditions of "tight" glycemic control in either Type 1 or Type 2 diabetes mellitus.

As is customary at such meetings, you will also be asked if, on the basis of the data presented and contained in the briefing documents, you recommend approval of pramlintide for the proposed indications. Type 1 and Type 2 diabetes are distinct clinical and pathophysiological conditions, and to the extent that the safety and efficacy outcomes are not the same for both groups studied, we will ask for your advice on the approvability of the drug for each condition separately. In addition, FDA is concerned, on the basis of its review, about the risk of severe hypoglycemia with pramlintide. We will ask for your input on labeling in this regard, should the drug eventually be approved.

Finally, we will ask for input on what, if any, additional studies are necessary, either pre-approval or post-approval.

As part of the Advisory Committee process, the review divisions of CDER routinely provide briefing packages including copies of relevant reviews and other materials to the members of the Committee (and to the sponsor) in advance of the public meeting and according to a carefully defined timeline. In addition, CDER is committed to providing, as much as is possible, completed or nearly completed review documents, which often will contain statements of preliminary reviewer opinion based on the data submitted as well as recommendations for regulatory action.

Members of the Advisory Committee, the public, as well as representatives of the company should understand that the opinions expressed in the reviews contained in the briefing packet represent opinions of the individual reviewer(s), rendered after review of one or more sections of the NDA, but without the influence of extensive internal Division or Agency discussion and, obviously, without the benefit, in this case, of the presentations to and deliberations by the Metabolic and Endocrine Advisory Committee. These opinions do not represent final Agency judgment nor do they reflect actual or planned Agency regulatory action on the application. Finally, co-signature by the reviewers' immediate supervisors does not imply complete concurrence with recommendations and opinions but rather signifies that the review document and the body of regulatory work that it represents are satisfactory and that therefore the review is acceptable for inclusion in the file and in the briefing packet for the Advisory Committee.

The purpose of the Advisory Committee meeting is to provide an open public forum for unbiased, scientifically-based presentation and discussion of the relevant safety and efficacy information contained in the sponsor's NDA. The FDA convenes these meetings in order to garner the views and comments of outside, non-conflicted experts in the field. We enter into the meeting prepared by our own review of the NDA and of the sponsor's briefing materials, but without a predetermined decision about a course of regulatory action. We identify areas of interest or concern and make every effort to direct our specific questions to the committee to address those areas. We believe we have done so for the upcoming meeting on Symlin. We look forward to an open discussion of the scientific merits of the clinical investigations of Symlin in patients with Type 1 and Type 2 diabetes and of the specifics of the data generated from these studies.